

Pharmacokinetics of a Novel EVG / COBI / FTC / GS-7340 Single Tablet Regimen

S Ramanathan, X Wei, J Custodio,
H Wang, A Dave, A Cheng, and
B Kearney

Gilead Sciences, Inc., USA

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Abstract #O_13

GS-7340: Novel Prodrug of Tenofovir (TFV) Designed to Deliver TFV to Cells

Gut Lumen

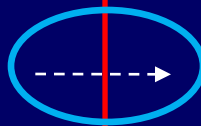
Blood

Lymphocytes

TDF
(Viread®)



TDF



TDF

↓
TFV



↓
TFV

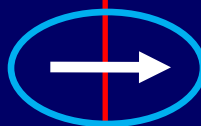


TFV-DP

GS-7340



GS-7340



GS-7340

↓
TFV



↓
TFV



TFV-DP

GS-7340 Profile

- In Vitro Features vs TDF
 - Greater potency and ~200-fold more stable in plasma: circulating prodrug
 - Rapidly metabolized by Cathepsin A in lymphoid cells
- Antiviral Activity vs TDF as monotherapy
 - GS-7340 \geq 25 mg QD provides greater HIV-1 RNA drop (1.5 to 1.7 \log_{10} c/ml) vs TDF (~0.9)
- Pharmacokinetics vs TDF
 - Circulating plasma exposures of GS-7340 (~ 5 hrs post-dose)
 - 7- fold higher TFV-DP in PBMC at 1/10th TDF dose
 - ~90% lower circulating TFV in plasma
- Potential for new single-tablet regimens (STRs) with a range of HIV drug classes
 - EVG/COBI/FTC/TDF (QUAD) highly efficacious and well tolerated in Phase 3 studies of treatment-naïve patients

Elvitegravir/Cobicistat/Emtricitabine/GS-7340

- EVG/COBI/FTC/GS-7340 assessment from three Phase 1 studies
 - Multiple dose PK of EVG/COBI/FTC/**GS-7340 STR**
 - Drug interaction potential between GS-7340 and COBI
 - Selection of GS-7340 dose for STR clinical development
- Study Designs
 - Study 1
 - 4 x 4 crossover of EVG/COBI/FTC/**GS-7340 25 mg or 40 mg**, EVG/COBI/FTC/TDF (QUAD) and GS-7340 single agent 25 mg
 - Study 2
 - Fixed sequence crossover: GS-7340 8 mg alone, with COBI 150 mg
 - Study 3
 - Two, 2-way crossover cohorts
 - Cohort 1: EVG/COBI/FTC/**GS-7340 10 mg**, EVG/COBI
 - Cohort 2: EVG/COBI/FTC/**GS-7340 10 mg**, FTC/GS-7340 25 mg

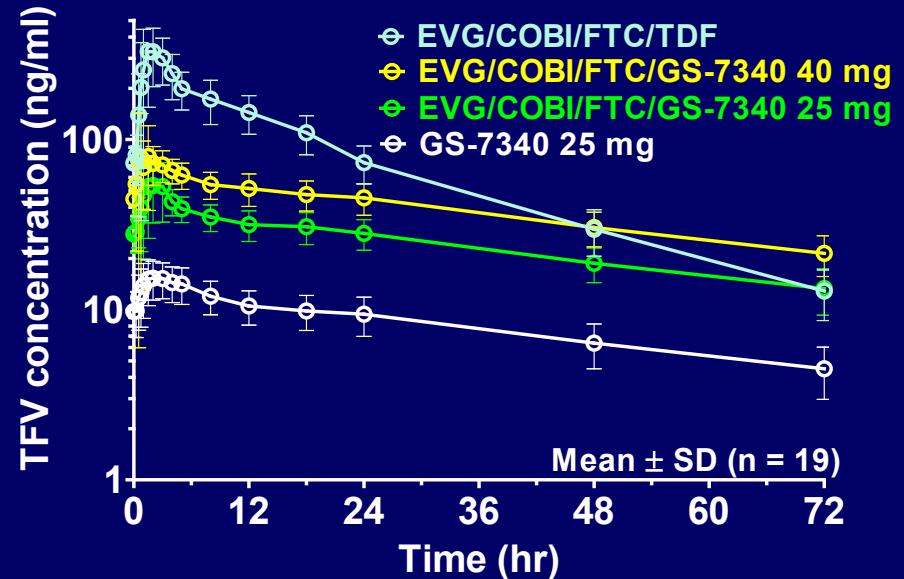
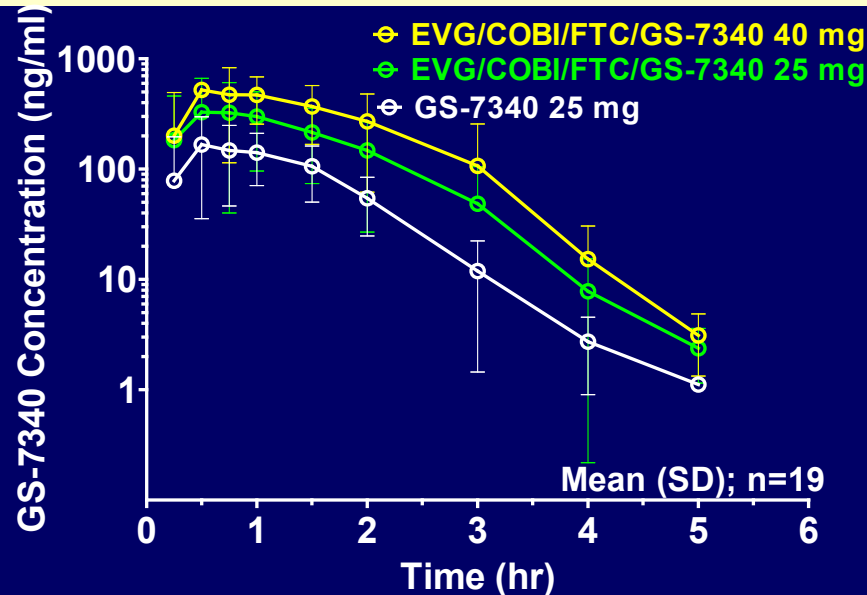
Demographics and Safety

	Study 1 (n=20)	Study 2 (n=12)	Study 3 (n=34)
Gender	10 males 10 females	8 males 4 females	24 male 10 female
Age (yrs) Mean (range)	37 (25-45)	33 (22-44)	32 (18-45)
Weight (kg) Mean (range)	80.2 (63.2-102)	78.5 (64.0-105)	74.9 (46.6-104)
Race	17 White 3 Black	9 White 3 Black	20 White 14 Black

- All treatments were generally well tolerated
- No Grade 3/4 adverse events observed across studies
- One discontinuation in Study 1 due to AE (Grade 2 rhabdomyolysis) while receiving GS-7340 25 mg

Study 1 Results: GS-7340 and Tenofovir PK

STR with GS-7340 25 mg or 40 mg

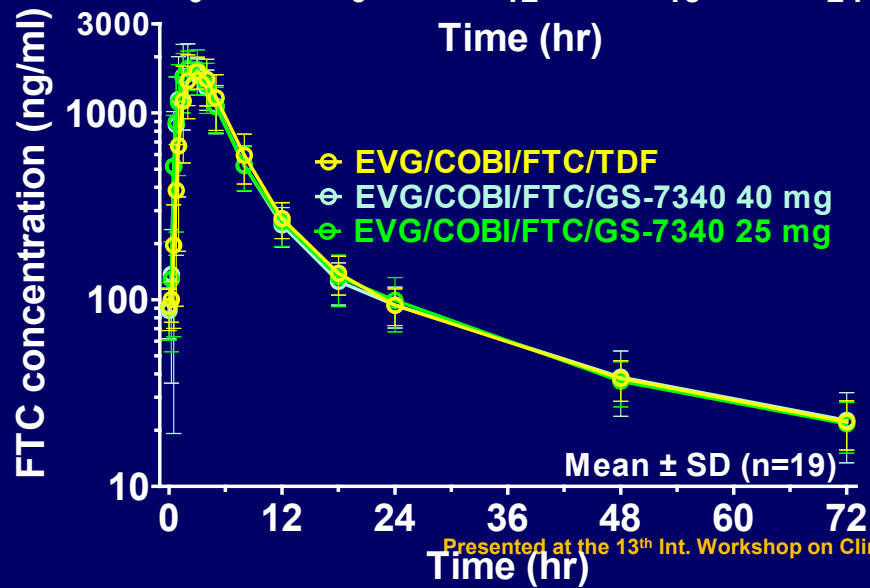
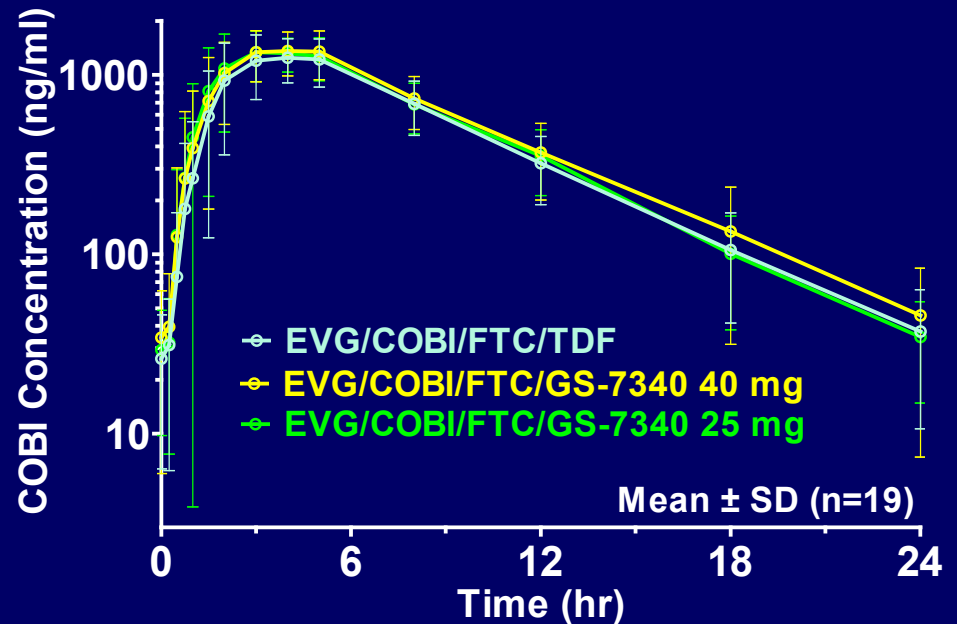
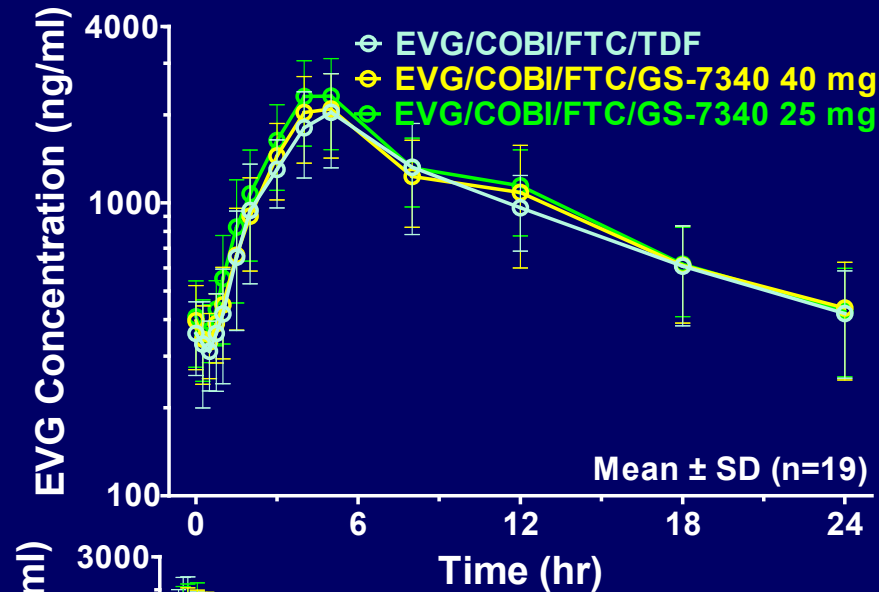


Mean (%CV)	GS-7340			Tenofovir			
	STR 25 mg	STR 40 mg	GS-7340 25 mg	STR 25 mg	STR 40 mg	GS-7340 25 mg	Quad
AUC (ng.hr/ml)	552 (41)	930 (34)	242 (42)	835 (18)	1300 (21)	273 (24)	3740 (22)
C _{max} (ng/ml)	507 (54)	793 (52)	215 (55)	66 (51)	103 (64)	16 (25)	445 (29)
C _{tau} (ng/ml)	-			28 (20)	45 (21)	9.4 (26)	73 (25)

- GS-7340 and TFV plasma exposures higher as STR vs GS-7340 alone

Study 1 Results: EVG, COBI, and FTC PK

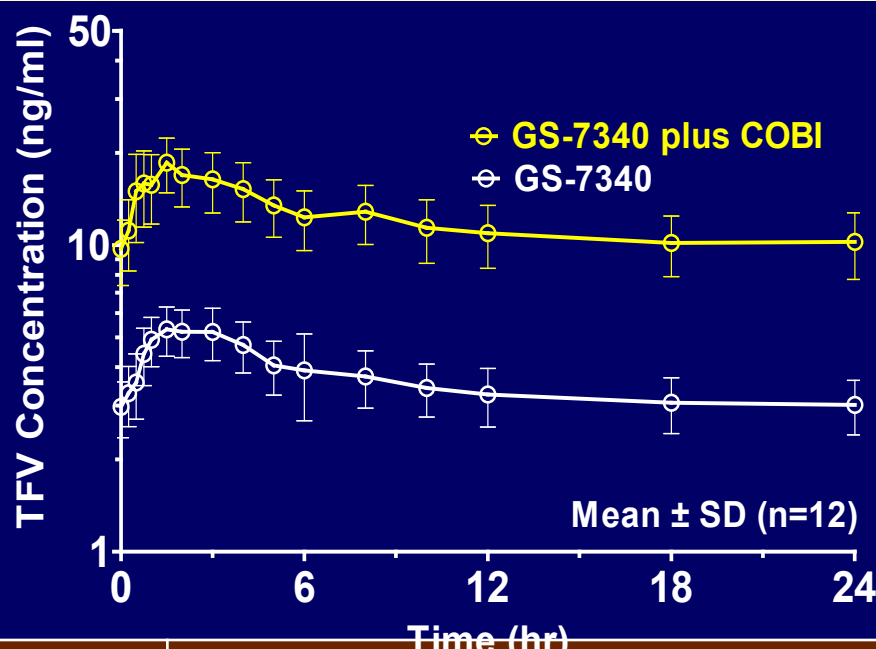
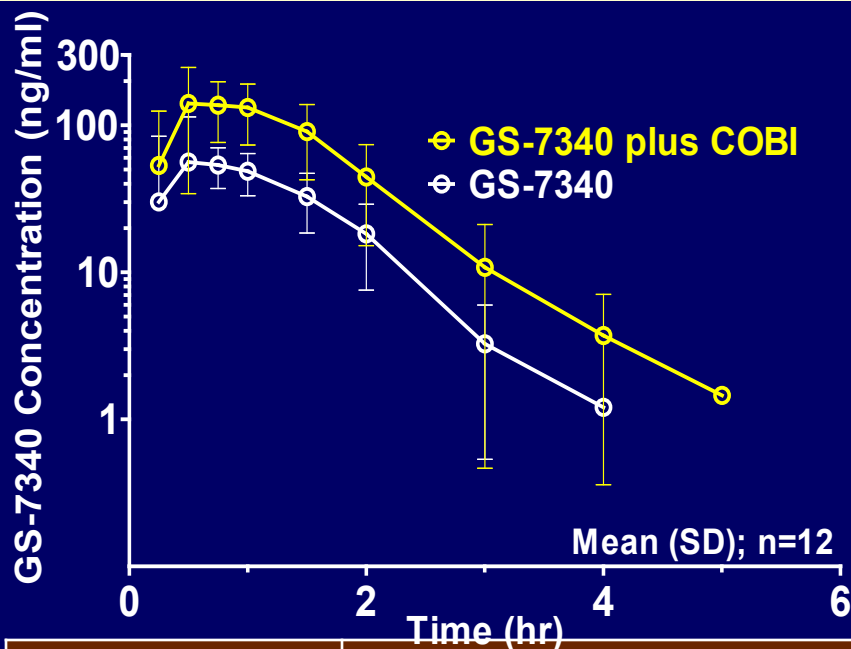
STR with GS-7340 25 mg or 40 mg



- EVG, COBI, and FTC PK similar between **GS-7340 STR** and **QUAD**

Study 2 Results: GS-7340 and Tenofovir PK

GS-7340 8 mg with COBI 150 mg

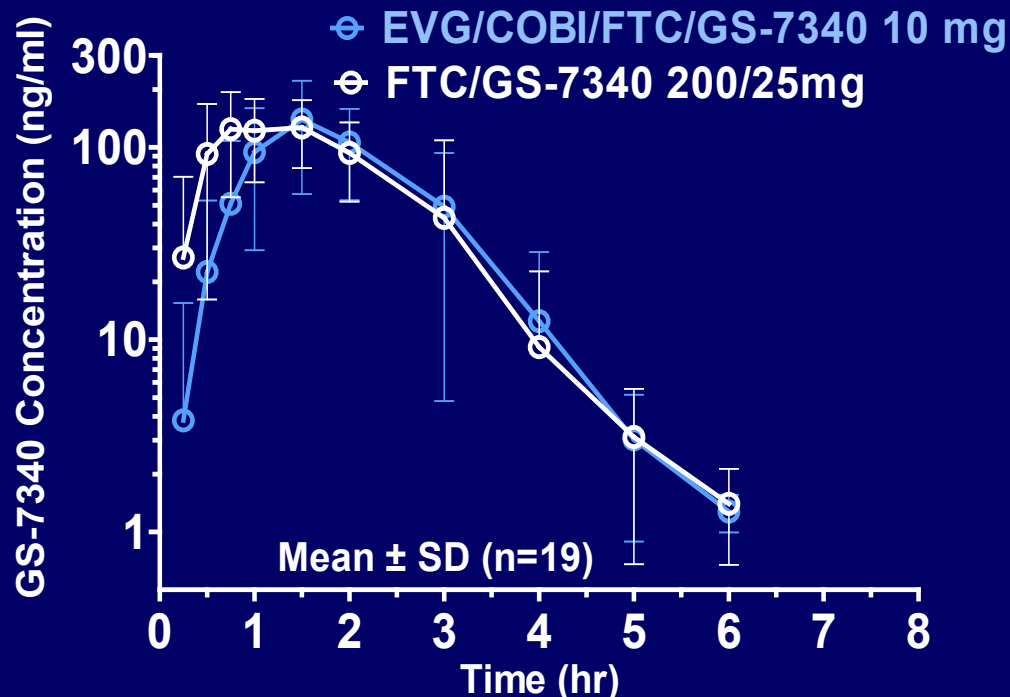


Mean (%CV)	GS-7340		Tenofovir	
	GS-7340 8 mg plus COBI	GS-7340 8 mg	GS-7340 8 mg plus COBI	GS-7340 8 mg
AUC (ng.hr/ml)	188 (27)	81 (44)	287 (22)	86 (19)
C _{max} (ng/ml)	142 (33)	71 (73)	19 (21)	5.8 (20)
C _{tau} (ng/ml)			10 (24)	3.0 (20)

• GS-7340 STR findings driven by COBI (inhibition of intestinal Pgp-efflux)

Study 3 Results: GS-7340 PK

STR with GS-7340 10 mg

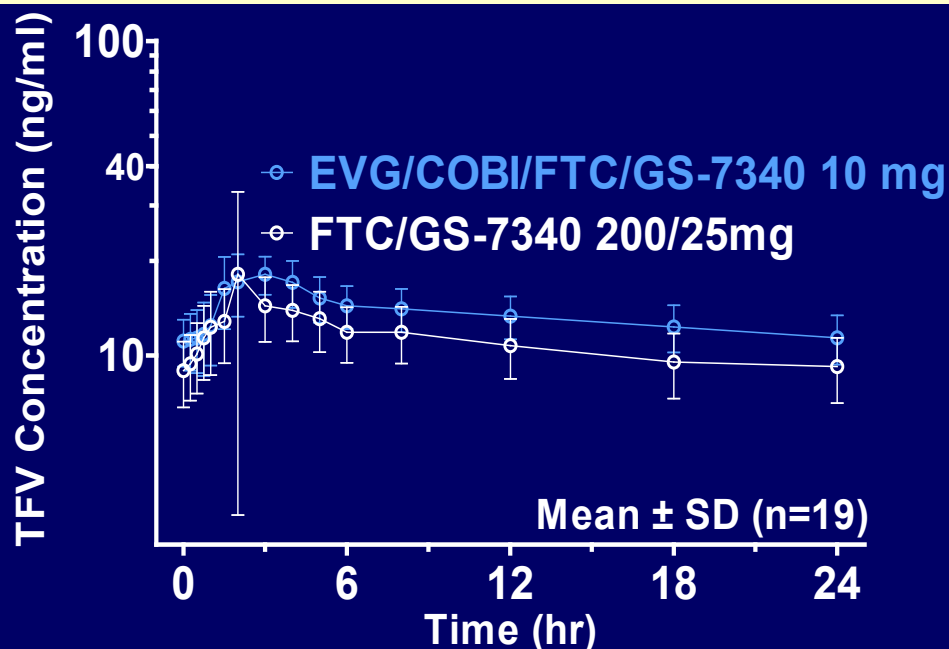


GS-7340 PK Parameter Mean (%CV)	STR 10 mg	FTC/GS-7340 25 mg	GMR (90% CI)
AUC_{last} (ng.hr/ml)	250 (25)	278 (29)	91.4 (84.1,99.4)
C_{max} (ng/ml)	177 (35)	180 (34)	98.7 (84.6,115)

• STR with GS-7340 10 mg provides similar exposures as GS-7340 25 mg

Study 3 Results: Tenofovir PK

STR with GS-7340 10 mg

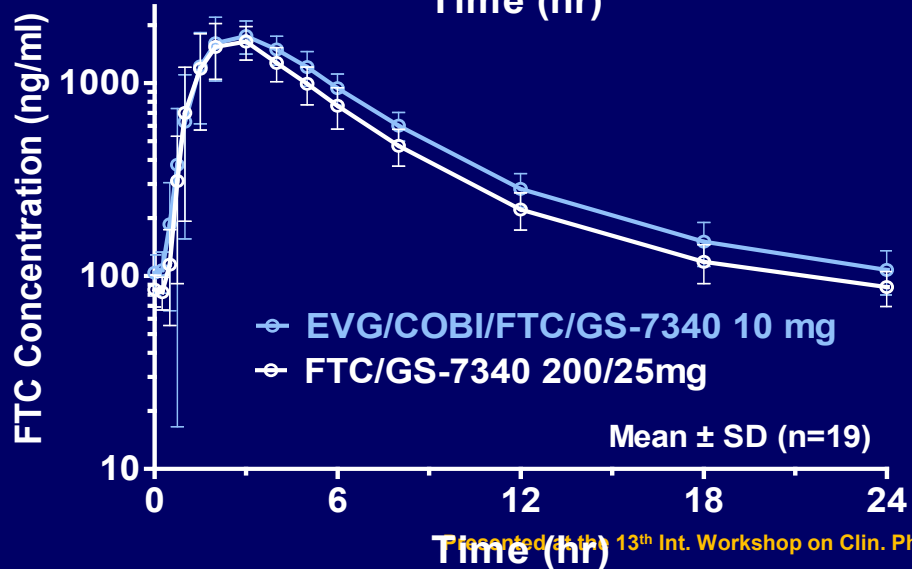
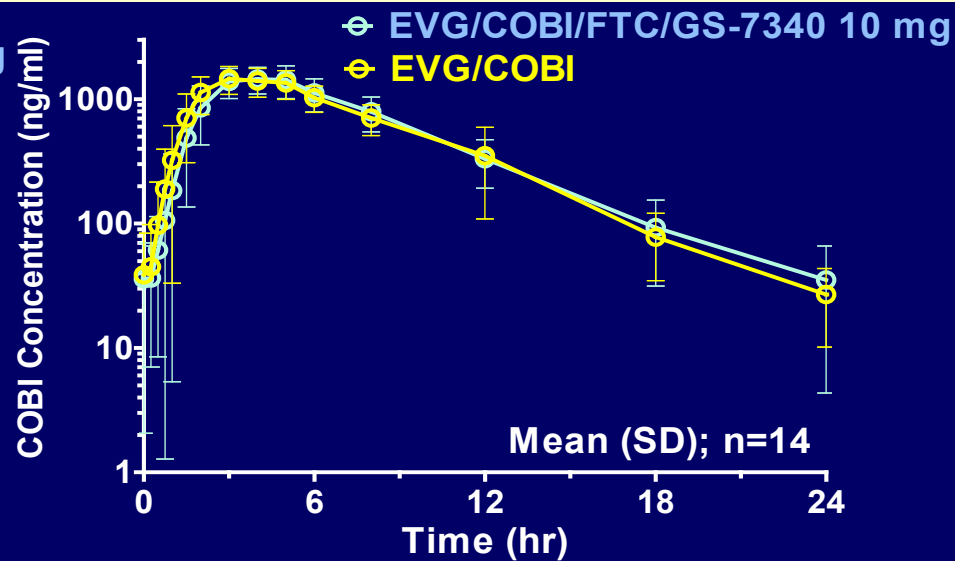
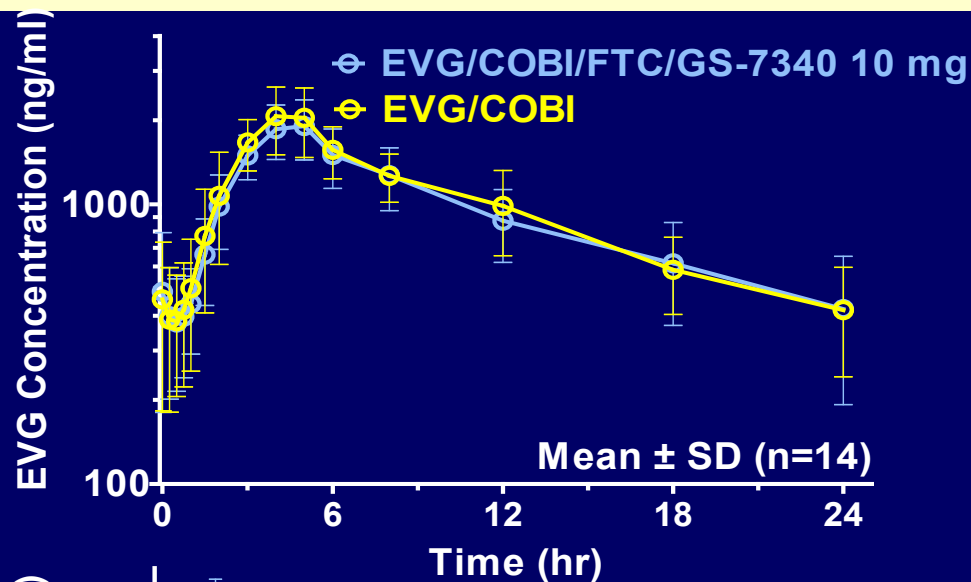


TFV PK; Mean (%CV)	STR 10 mg	FTC/GS-7340 25 mg	GMR (90% CI)
AUC_{τ} (ng.hr/ml)	324 (15)	266 (22)	124 (117,131)
C_{\max} (ng/ml)	20 (14)	19 (76)	114 (97.5,134)
C_{τ} (ng/ml)	11 (18)	9.2 (24)	125 (118,134)

STR with GS-7340 10 mg: Comparable TFV vs GS-7340 25 mg; 90% lower TFV exposure vs QUAD

Study 3 Results: EVG, COBI and FTC PK

STR with GS-7340 10 mg



- EVG, COBI, and FTC PK similar between GS-7340 STR and EVG/COBI or FTC single agent

Conclusions

- GS-7340 and TFV exposures ~2-3-fold higher with COBI or as EVG/COBI/FTC/GS-7340 STR
 - Driven by COBI inhibition of intestinal Pgp-mediated intestinal secretion of GS-7340
- EVG/COBI/FTC/GS-7340 10 mg provided comparable GS-7340 and TFV PK as GS-7340 25 mg, ~90% lower TFV exposure vs QUAD
- EVG/COBI/FTC/GS-7340 STR provided similar EVG, COBI, and FTC PK vs single agents (EVG/COBI and FTC)
- A Phase 2 study comparing EVG/COBI/FTC/GS-7340 STR vs QUAD ongoing